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OZONE HEALTH EFFECTS AND EMERGING ISSUES IN RELATION TO STANDARDS SETTING

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ABSTRACT

Our current knowledge of O_3 exposure and health effects is growing rapidly. Transient respiratory function effects accumulate throughout an exposure day, and ambient exposures have broad daily peaks. O_3 exposures also produce changes in airway inflammation and permeability. Healthy adults engaged for ~ 1/2 hr in outdoor exercise show greater responses than those observed in chamber studies involving 1 or 2 hr of exposure, indicating potentiation of the O_3 response by other environmental exposures. Acute animal studies show biochemical and structural responses to O_3 are potentiated by co-exposure to NO_2 and H_2SO_4. Chronic animal studies show that O_3 effects on lung structure accumulate, and several recent epidemiological studies suggest that cumulative functional effects are occurring in people. Recent research has also shown: 1) a seasonal variation in functional responsiveness in humans; 2) that a seasonal pattern of daily exposure in monkeys produces greater changes in the lung than a continuous pattern of daily exposures at the same concentration; and 3) that transient exposures produce persistent responses.

OZONE HEALTH EFFECTS

Ozone (O_3) exposure affects the structure and function of the respiratory tract in a variety of ways. Most of the research on humans has focussed on its effects on respiratory function, especially on transient responses to acute exposures. Other lung functional responses to acute and subacute exposures which have been studied, largely in animals, include mucociliary and early alveolar zone particle clearance, functional responses in macrophages and epithelial cells, and changes in lung cell secretions. Structural changes in the vicinity of the respiratory acinus have been associated with subchronic and chronic animal exposure protocols. However, the health significance of localized structural changes, and the roles of the transient functional and

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[illegible] and identifies critical knowledge gaps in the relationships between the observed effects and lung disease.

Transient Effects on Respiratory Function

It is well established that the inhalation of O_3 causes concentration dependent mean decrements in volumes and flow rates during forced expiratory maneuvers, and that the mean decrements increase with increasing minute ventilation [ref. 1], that there is a wide range of reproducible responsiveness among healthy subjects [ref. 2], and that functional responsiveness to O_3 is no greater, and usually lower, among cigarette smokers [refs. 3,4], older adults [refs. 5,6], asthmatics [refs. 7,8], and patients with allergic rhinitis [ref. 9] or chronic obstructive pulmonary disease (COPD) [refs. 10,11]. It is also well established that repetitive daily exposures, at a level which produces a functional response upon single exposure, results in an enhanced response on the second day but diminishing responses on days 3 and 4, with virtually no response by day 5 [refs. 12-14]. This functional adaptation disappears about a week after exposure ceases [refs. 15,16].

The current U.S. National Ambient Air Quality Standard (NAAQS) for O_3 uses a 1 hr averaging time, based primarily on a report of respiratory function impairment for exercising persons exposed for 1 hr at 0.15 ppm [ref. 17], and the expectation that ambient exposures are characterized by relatively sharp afternoon peaks. However, it has recently been shown that ambient O_3 concentrations in the Netherlands and New Jersey often have broad daytime peaks, with maximum 8 hr averages close to 90% of peak 1 hr levels [ref. 18]. In the ambient air in the U.S. as a whole, a 1 hr O_3 peak at 0.12 ppm is, on average, associated with a maximum 8 hr average concentration of 0.10 ppm. Approximately half of the U.S. population lives in communities which exceed the current O_3 NAAQS at least twice annually, and many communities in California frequently have concentrations exceeding 0.2 ppm [ref. 19].

The first indications that the effects of O_3 on respiratory function accumulate over more than 1 hr were the observations of McDonnell et al. [ref. 20] and Kulle et al. [ref. 21] in chamber exposures to O_3 in purified air for 2 hr. Significant function decrements observed after 2 hr of exposure were not present at measurements made after 1 hr.

Spektor et al. noted that children at summer camps with active outdoor recreation programs had greater lung function decrements than children exposed to O_3 at comparable concentrations in chambers for 1 or 2 hr [ref. 22]. Furthermore, their activity levels, although not measured, were known to be considerably lower than those of the children exposed in the chamber studies. Since it is well established that functional responses to O_3 increase with levels of physical activity and ventilation [ref. 1], the greater responses in the camp children had to be caused by other factors, such as greater cumulative exposure, or to the potentiation of the response to O_3 by other pollu-

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tants in the ambient air. Cumulative daily exposures to O_3 were generally greater for the camp children exposed all day long than for the children exposed in chambers for a 1 or 2 hr period preceded and followed by clean air exposure.

Similar considerations apply to the recent study of Kinney et al. [refs. 23,24] of school children in Kingston and Harriman, TN whose lung function was measured in school on up to six occasions during a 2 mo period in the late winter and early spring. Child specific regressions of function versus max 1 hr O_3 during the previous day indicated significant associations between O_3 and function, with coefficients similar to those seen in the summer camp studies of Lippmann et al. [ref. 25] and Spektor et al. [ref. 22]. Since children in school may be expected to have relatively low activity levels, the relatively high response coefficients may be due to potentiation by other pollutants, or to a low-level of seasonal adaptation. As shown by Spengler et al. [ref. 26], Kingston-Harriman has higher annual average and peak acid aerosol concentrations than other cities studied, i.e., Steubenville, OH, St. Louis, MO, and Portage, WI. Alternatively, the relatively high response coefficients could have been due to the fact that the measurements were made in the late winter and early spring. Hackney [ref. 27] has shown evidence for a seasonal adaptation, and children studied during the summer may not be as responsive as children measured earlier in the year.

In the study by Hackney [ref. 27] at Rancho Los Amigos Hospital in Southern California, a group of subjects selected for their relatively high functional responsiveness to O_3 had much greater functional decrements following 2 hr of exposure to O_3 at 0.18 ppm with intermittent exercise in a chamber in the spring than they did in the following autumn or winter, while their responses in the following spring were equivalent to those in the preceding spring. These findings suggest that some of the variability in response coefficients reported for earlier controlled human exposures to O_3 in chambers could have been due to seasonal variations in responsiveness which, in turn, may be related to a long-term adaptation to chronic O_3 exposure.

The observations from the field studies in the children's camps stimulated Folinsbee et al. [ref. 28] at the EPA Clinical Studies Laboratory in Chapel Hill, NC to undertake a chamber exposure study of adult volunteers involving

following day. The functional decrements after 6.6 hrs of exposure at 0.12 ppm were comparable to those seen previously in the same laboratory on similar subjects following 2 hr of intermittent heavier exercise at an interpolated concentration of ~ 0.22 ppm. The total amount of O_3 inhaled during 2 hr of intermittent heavy exercise @ 0.22 ppm would be ~ 2.0 mg O_3. The corresponding amount of O_3 inhaled during 6.6 hr of intermittent moderate exercise @ 0.12 ppm was ~ 3.0 mg O_3. Thus, the effect accumulates with time, but there appears to be a concurrent temporal decay of effect. Follow-up studies in the same laboratory at 0.08, 0.10, and 0.12 ppm confirmed the previous findings, with the 0.08 and 0.10 ppm exposures producing lesser changes which also became progressively greater after each hour of exposure [ref. 29]. Thus, it is now clear that the appropriate averaging time for transient functional decrements caused by O_3 is $\geq$ 6 hr, and there is no scientific basis for a 1 hr health based exposure limit. Since O_3 exposures in ambient air can have broad peaks with 8 hr averages equal to ~ 90% of the peak 1 hr averages, the functional decrements associated with ambient concentrations are likely to be much greater than those predicted on the basis of the responses in the chamber studies following 1-2 hr exposures.

To the extent that transient changes in respiratory function influence the selection of a NAAQS, the case for a longer term acute exposure standard is quite clear. The remaining question now has become whether there is any scientific rationale for retaining a 1 hr standard to supplement the clearly needed new standard with an averaging time on the order of 8 hr.

A study which addressed the issue of the potentiation of the characteristic functional response to inhaled O_3 by other environmental cofactors was performed at the NYU Medical Center in Tuxedo, NY on healthy adult nonsmokers engaged in a daily program of outdoor exercise. The ambient mixture contained low concentrations of acidic aerosols and NO_2 as well as O_3. Each subject did the same exercise each day, but exercise intensity and duration varied widely between subjects. Spirometry was performed immediately before and after each exercise period. O_3 concentrations during exercise ranged from 0.021 to 0.124 ppm. All measured functional indices showed significant ($p<0.01$) O_3 associated mean decrements. The functional decrements were similar, in proportion to lung volume, to those seen in children engaged in supervised recreational programs in summer camps, and about twice as large as those seen in controlled 1 and 2 hr exposures in chambers. Since the ambient exposures of the adults exercising out of doors were for ~ 1/2 hr, it was concluded that ambient cofactors potentiate the responses to O_3 [ref. 30]. Thus, the results of the exposures in chambers to O_3 in purified air can underestimate the O_3 associated responses which occur among populations engaged in normal outdoor recreational

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The NYU study on exercising adults, and earlier studies on children at summer camps [refs. 22,24,31] were not able to demonstrate the specific effect of any of the measured environmental variables, including heat stress and acid aerosol concentration, on the O_3-associated responses. The inability to show the individual effects of other environmental cofactors on the response to ambient O_3 may be due to inadequate knowledge on the appropriate biological averaging time for these other factors. However, in the study of functional responses of children to ambient pollution in Mendham, NJ, a weeklong baseline shift in PEFR was associated with both O_3 and H_2SO_4 exposures during a four day pollution episode which preceded it [ref. 31]. A similar response to a brief episode with elevated O_3 and a much higher peak 4 hr concentration of H_2SO_4 (46 $\mu g/m^3$) was seen among girls attending a summer camp in 1986 at Dunnville, Ontario, Canada, on the northeast shore of Lake Erie [ref. 32].

Controlled human exposure studies in chambers have not demonstrated synergism in functional response between O_3 and NO_2 or H_2SO_4, although Stacy et al. [ref. 33] reported mean responses to 0.40 ppm O_3 and 100 $\mu g/m^3$ H_2SO_4 after 2 hr of exposure of -9.0% for FVC and -11.5% for FEV_1, compared to -5.7 and -7.7% for O_3 alone, -1.4, and -1.2% for sham exposure, and +0.9 and +0.9% for H_2SO_4 alone. These mean differences, which appear to indicate an enhancement of the O_3 response by H_2SO_4, were not statistically significant because of the very high variability of the sham exposure results. Pollutant interactions which potentiate the characteristic O_3 response have been reported for other effects, in controlled exposure studies in animals, as will be discussed later in the sections on lung defenses and lung structure.

Exposure to O_3 can also alter the responsiveness of the airways to other bronchoconstrictive challenges as measured by changes in respiratory mechanics. For example, Folinsbee et al. [ref. 28] reported that airway reactivity to methacholine for the group of subjects as a whole was approximately doubled following 6.6 hr exposures to 0.12 ppm O_3. Airway hyperresponsiveness (to histamine) had previously been demonstrated, but only at O_3 concentrations $\geq$ 0.4 ppm [refs. 34,35]. On an individual basis, Folinsbee et al. found no ap-

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Effects on Lung Defenses and Lung Structure

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that can be collected on the effects of O_3 on lung defenses and lung structure. Most of the limited body of data on humans that are available relate to the rate of particle clearance from the lungs and to alterations in the constituents of bronchoalveolar lavage (BAL).

Foster et al. [ref. 37] studied the effect of 2 hr exposures to 0.2 or 0.4 ppm O_3 with intermittent light exercise on the rates of tracheobronchial mucociliary particle clearance in seven healthy adult males, using γ-tagged inert particles and external detection with a γ-camera. The 0.4 ppm O_3 exposure produced a marked acceleration in particle clearance from both central and peripheral airways, as well as a 12% drop in FVC. The 0.2 ppm O_3 exposure produced a significant acceleration of particle clearance only in peripheral airways, and a small and nonsignificant reduction in FVC.

The effects of O_3 on mucociliary particle clearance have also been studied in animals. Rats exposed for 4 hr to O_3 at 0.4 to 1.2 ppm exhibited slowed clearance at $\geq$ 0.8 ppm, but not at 0.4 ppm [refs. 38,39]. Rabbits exposed for 2 hr at 0.1, 0.25 and 0.6 ppm O_3 showed a concentration dependent trend of reduced clearance rate with increasing concentrations, with the change at 0.6 ppm being ~ 50% and significantly different from control [ref. 40]. It is not known why the animal tests show only retarded mucociliary clearance in response to O_3 exposure, while the human tests show accelerated clearance. In corresponding tests with other irritants, i.e., H_2SO_4 aerosol and cigarette smoke, both humans and animals have exhibited accelerated clearance at lower exposures and retarded clearance at higher exposures [ref. 41].

Studies of the effects of O_3 on alveolar macrophage mediated particle clearance during the first few weeks have also been performed in rats and rabbits. Rats exposed for 4 hr to 0.8 ppm O_3 had accelerated particle clearance [refs. 38,39]. Rabbits exposed to 0.1, 0.6, or 1.2 ppm O_3 once for 2 hr had accelerated clearance at 0.1 ppm and retarded clearance at 1.2 ppm. Rabbits exposed for 2 hr/d for 13 days at 0.1 or 0.6 ppm O_3 had accelerated clearance for the first 10 days, with a greater effect at 0.6 ppm [ref. 42].

The permeability of the respiratory epithelium can be determined by measuring the plasma concentration of horseradish peroxidase (HRP) after intratracheal instillation [ref. 43]. Miller et al. [ref. 44] showed that 2 hr exposures @ 1 ppm O_3 affected permeability in the guinea pigs using this technique. Permeability can also be determined from the externally measured rate of clearance from the lung of γ-emitting ^{99m}Tc diethylenetriaminepentaacetate (^{99m}Tc-DTPA), inhaled as a droplet aerosol or instilled via the trachea. Bhalla et al. [refs. 45,46] reported increased transfer of instilled tracers from the bronchoalveolar lumen to blood following 2 hr exposure of rats to 0.6 and 0.8 ppm O_3. Bhalla et al. [ref. 46] also examined the effects of exercise

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and co-exposure to other pollutants on tracheal and bronchoalveolar permeability. Atmospheric mixtures included: O_3 + NO_2 at 0.6 ppm and 2.5 ppm, respectively; and a 7-component particle and gas mixture (complex atmosphere) representing urban air pollution in a photochemical environment. The effects of exercise during exposure were evaluated by exposing additional groups in an enclosed treadmill. Exposure of resting rats to 0.8 ppm O_3 increased tracheal permeability to DTPA and bronchoalveolar permeability to DTPA and bovine serum albumin (BSA) at 1 hr after the exposure. Bronchoalveolar, but not tracheal, permeability remained elevated at 24 hr after the exposure. Exercise during exposure to O_3 increased permeability to both tracers in the tracheal and the bronchoalveolar zones, and prolonged the duration of increased permeability in the tracheal zone from 1 hr to 24 hr, and in the bronchoalveolar zone from 24 hr to 48 hr. Exposure at rest to 0.6 ppm O_3 plus 2.5 ppm NO_2 significantly increased bronchoalveolar permeability at 1 and 24 hr after exposure although exposure at rest to 0.6 ppm O_3 alone increased bronchoalveolar permeability only at 1 hr after exposure. Exposure to O_3 and NO_2 during exercise led to significantly greater permeability to DTPA than did exercising exposure to O_3 alone. Resting rats exposed to the complex gas/aerosol atmosphere had increased permeability at 1 and 24 hr after exposure. Nitric acid vapor was formed in both the O_3 + NO_2 atmosphere and the complex gas/aerosol atmosphere. The particles in the latter also contained hydrogen ions equivalent in concentration to about 100 g/m^3 of NH_4HSO_4, suggesting that acidic components in the atmospheres produced effects that were additive upon the effect of O_3 in producing both increase and prolongation of permeability in tracheal and bronchoalveolar zones of the respiratory tract.

Intravenous injection of tracer molecules and recovery of the label in lung lavage fluid can also be used to identify lung injury and loss of integrity of air-blood barrier after exposures to low levels of toxic agents [refs. 47,48]. The increase in permeability from blood to air was comparable to the increase from air to blood [ref. 45]. Autoradiography by electron microscopy identified multiple pathways for BSA transfer from blood to the alveolar space. Although defects in tight junctions of alveolar type I cells were

measured 75 min after the exposures by lung imaging with a γ-camera. O_3 exposure caused respiratory symptoms in all 8 subjects and was associated with a 14 ± 2.8% (mean ± S.E.) decrement in FVC ($p < 0.001$) and a 71 ± 22% increase in SR_{aw} ($p = 0.04$). Compared with the air exposure day, 7 of the 8 subjects showed increased ^{99m}Tc-DTPA clearance after the O_3 exposure with the mean value increasing from 0.59 ± 0.08 to 1.75 ± 0.43%/min ($p = 0.03$). Thus, O_3 exposure sufficient to produce decrements in the respiratory function of human subjects also caused increased ^{99m}Tc-DTPA clearance.

The Overton and Miller [ref. 50] model of O_3 dosimetry within the lungs predicts similar airway deposition patterns for O_3 in rats and humans, with the greatest deposition in the vicinity of the respiratory acinus. A recent extension of this work, based upon differences in O_3 removal in the upper respiratory tract and fraction exhaled, suggests that humans have about twice the deposition rate at the respiratory acinus as rats [ref. 51]. Thus, the effects seen in the chronic animal inhalation studies are likely to be conservative estimates of the effects that occur in humans in areas with high chronic exposure, such as Southern California.

Most of the inhaled O_3 penetrates beyond the sites in the airways which trigger the functional responses and produces effects which are concentrated on the region at and just beyond the terminal bronchioles. These include changes in biochemical indices and lung structure. In this region, the effects of O_3 exposure in terms of progressive epithelial damage and inflammatory changes appear to be cumulative and persistent, even in animals that have adapted to the exposure in terms of respiratory mechanics [ref. 52].

In groups of mice exposed to 0.2 ppm O_3 for 1, 3, or 6 hr, superoxide anion radical production decreased 8, 18, and 35% respectively, indicating a progressive decrease in bacteriocidal capacity with increasing duration of exposure [ref. 53]. In inhalation studies in rats involving O_3 exposures at constant concentrations of 0.12 and 0.25 ppm for 12 hr/d for 6 and 12 wk, Barry et al. [ref. 54] found that hyperplasia of Type I alveolar cells in the proximal alveoli was linearly related to the cumulative lifetime O_3 exposure.

For some chronic effects, intermittent exposures can produce greater effects than those produced by a continuous exposure regime which results in higher cumulative exposures. For example, Tyler et al. [ref. 55] exposed two groups of 7 mo old male monkeys to 0.25 ppm O_3 for 8 hr/d either daily or, in the seasonal model, on days of alternate months during a total exposure period of 18 mo. A control group breathed only filtered air. Monkeys from the seasonal exposure model, but not those exposed daily, had significantly increased total lung collagen content, chest wall compliance, and inspiratory capacity. All monkeys exposed to O_3 had respiratory bronchiolitis with significant in-

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Epidemiologic studies of populations living in Southern California suggest that chronic oxidant exposures do affect baseline respiratory function. Detels et al. [ref. 56] compared respiratory function at two times 5 yr apart in Glendora (a high oxidant community) and in Lancaster (a lower oxidant community-but not low by national standards). Baseline function was lower in Glendora, and there was a greater rate of decline over 5 yr. Kilburn et al. [ref. 57] reported that nonsmoking and exsmoking wives of Long Beach shipyard workers had significantly lower values of FEV_1, mid expiratory flow, terminal expiratory flow, and carbon monoxide diffusing capacity than those in a matched population from Michigan. The oxidant exposures in Long Beach and Michigan are not known, but those in Long Beach and Lancaster are similar, while those in Michigan are generally much lower. Both studies have some serious methodologic deficiencies, but deserve citation because they suggest effects which are consistent with the chronic animal exposure findings.

A variety of pollutant interactions which potentiate other characteristic O_3 responses have been reported in studies in animals. Last [ref. 58] reported significant synergistic interaction in rats, in terms of increased lung protein content, after 9 d exposures at 0.2 ppm O_3 with 20 or 40 $\mu g/m^3$ H_2SO_4, and a non-significant increase for 9 d at 0.2 ppm O_3 with 5 $\mu g/m^3$ H_2SO_4. Kleinman et al. [ref. 59] reported that O_3-induced lesions in the lung parenchyma were greater in size in rats also exposed to either H_2SO_4 or NO_2. Graham et al. [ref. 60] reported a synergistic interaction between O_3 and NO_2 in terms of mortality in mice challenged with streptococcal infection either immediately or 18 hr after pollutant exposure. Pinkerton et al. [ref. 61] reported that asbestos fiber clearance from the lungs of rats was reduced when the rats were also exposed to O_3. This increased fiber retention could increase the fibrogenic and carcinogenic risks of asbestos.

The ability of O_3 and other toxicants to act synergistically indicates that exposure limits for O_3 should include an extra margin of safety to acknowledge

that co-exposures among ubiquitous pollutants such as O_3, NO_2, H_2SO_4, and asbestos are likely to occur in ambient air and many work environments.

EMERGING ISSUES IN RELATION TO STANDARDS SETTING

The results of recent research have substantially expanded our knowledge of exposure-response for many of the various effects of O_3 on the respiratory tract. They have also provided a basis for enhanced appreciation of the factors affecting delivered dose, the duration and progression of effects, and the variations in responsiveness among individuals. At the same time, it is important to recognize that we still have a primitive understanding of the biological mechanisms for most of the effects of concern, and that we lack a consensus on the health significance and importance in the pathogenesis of disease of even the more completely described effects, such as transient changes in respiratory function. While the absence of an adequate mechanistic framework is unfortunate, there is still a need for public action on standards and measures to protect the public health based on current knowledge. The issues related to exposure standards which should and can be addressed effectively in the next few years with carefully conceived and well executed exposure-response studies are:

1) The influence of patterns of O_3 exposure on patterns of response- extending from transient changes in respiratory and particle clearance functions through airway inflammation, lung permeability, cellular changes at the respiratory acinus, to persistent changes in lung architecture associated with lung fibrosis and emphysema.

2) The influence of other environmental factors on responses to O_3. We need to know more about the influence of temperature, humidity, and co-exposures to NO_2, SO_2, HNO_3, acidic aerosols, inert aerosols and other widespread components of ambient air on responses to O_3, and the extent to which the sequence of the exposures affect the responses.

3) Host factors affecting responsiveness. We need to identify the host factors responsible for the very wide range of responsiveness to O_3 exposure among humans and animals. Specifically, we need a better appreciation of how factors such as airway size and structure and respiratory patterns affect O_3 uptake, and how biochemical and genetic variations among individuals affect the responses of exposed tissues and cells.

4) Interspecies variability in responses. We need to have a better appreciation of the similarities and differences in responses between humans and laboratory animals, and the ventilatory, structural, biochemical and genetic factors w
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genetic factors which control them, so that the results of studies in animals can be interpreted for their implications to human health, especially for the chronic changes resulting from repetitive exposures.

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